Are antihypertensive drugs associated with abdominal aortic aneurysms?

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Objective: **The aim of this study was to investigate the association between anti-hypertensive drugs, the risk of developing an abdominal aortic aneurysm (AAA), aortic wall stiffness, collagen turnover, and change in aortic diameter.**
Study Design, Setting and Methods: **Data on present medication, smoking status, and medical history of participants in two population-based aneurysm screening programs in the United Kingdom were collected by use of questionnaire. Aortic elasticity was measured by M-mode ultrasound scanning. A serum radioimmunoassay of the amino-terminal propeptide of type III procollagen was used to assess collagen turnover in one of the patient series.**
Results: **Data from 438 cases with an AAA >29 mm and 5373 controls were analyzed. Calcium-channel blockers were independently associated with AAA. The odds ratio of having an AAA was 2.6 (95% confidence interval [CI], 1.5-4.2) after adjusting for all relevant confounders. Other antihypertensive drugs showed no increased risk. No significant differences in growth rates were found in cases exposed to any of the main antihypertensive drugs. An increased collagen turnover was found in subjects receiving angiotensin-converting enzyme (ACE) inhibitors: 4.26 mg/L (95% CI, 3.73-4.79) compared with 3.62 mg/L (95% CI, 3.49-3.76) for subjects not receiving ACE inhibitors. No differences in type III collagen turnover was found with use of any other antihypertensive drug. The mean aortic wall stiffness was greater for all subjects exposed to calcium-channel blockers, whether with AAA or not: 25.1 arbitrary units (95% CI, 20.0-30.2) vs 19.3 (95% CI, 18.1-20.4)($P = .002$). By contrast, the mean stiffness for cases receiving ACE inhibitors was smaller than for those not receiving ACE inhibitors: 19.0 (95% CI, 13.9-24.0) vs 25.2 (95% CI, 23.0-27.4).**
Conclusions: **Calcium-channel blockers were an independent risk factor for the presence of an AAA and were associated with an increased arterial aortic wall stiffness. ACE inhibitors were associated with decreased stiffness and greater collagen turnover. No significant effects on the growth rate of small aneurysms were detected. (J Vasc Surg 2002;36: 751-7.)**

The structural integrity of the aortic wall depends to a large extent on the extracellular matrix proteins elastin and collagen.[1-3] A large body of evidence suggests that aneurysms are the result of a localized inflammatory process resulting in complex remodeling that involves both the synthesis and degradation of matrix proteins.[4-12] Elastases and collagenases belong to a family of structurally related enzymes named matrix metalloproteinases (MMPs). MMPs produced by inflammatory cells have been found in human aneurysmal aortas and are seen as the main mediators of ground substance degradation.[13-15] Various drugs have been shown to reduce experimental aortic aneurysms in animal models.[16-18] Recent research showed that the calcium-channel antagonist amlodipine potentiates elastase and can increase growth of aneurysms in an animal model.[19] Finally, some of the MMPs implicated in the metabolism of elastin or collagen, depend on zinc for their activity.[20-22] Captopril is a thiol that was specifically designed to bind the zinc at the active site of angiotensin-converting enzyme (ACE). Captopril and other ACE inhibitors may, therefore, influence the metabolism of matrix proteins.[22] This may have clinical implications, as it is well known that patients with aneurysms are more likely to have ischemic heart disease and hypertension than are individuals without aneurysms.[23] The type of antihypertensive treatment may have implications on the risk of developing and the expansion rate of AAAs. The primary outcome measures of this study were the association between antihypertensive medication and risk of having an AAA, as measured by the odds ratio. Secondary outcome measures were differences in aortic expansion, aortic wall stiffness, and collagen turnover between subjects exposed to antihypertensive medication and those not exposed.

METHODS

The data used in this study were collected in two prospective, longitudinal, population-based screening studies in Chichester and Huntingdon, United Kingdom.[24,25] Anteroposterior measurements of aortic diameter were used in both centers. although in Chichester the larger of the anteroposterior and transverse measurements was used as the defining diameter.[24] Methods of measurement of the aortic diameter have been described previous-

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Supported by the Anglia and Oxford Regional Health Authority and the British Heart Foundation.
Competition of interest: nil.
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0741-5214/2002/$35.00 + 0 **24/1/126550**
doi:10.1067/mva.2002.126550

ly.[26] A case was defined as a person with an infrarenal aortic diameter of ≥30 mm, and a control was defined as a person with an infrarenal aortic diameter of <30 mm. All cases and controls from Chichester were included in this study. The remainder of the subjects came from a screening program in Huntingdon. The cohort of screened men in the Huntingdon District over the age of 50 served as a basis for a nested case-control study. All cases still attending the screening program were selected for a case-control study and were invited to participate. Controls were selected at random from the screened population in Huntingdon with an aorta of <25 mm wide on the first screen, to allow for a clear distinction between cases and controls. Controls were matched for age using frequency matching. We did not use individual case-control matching.

Data about current smoking status, smoking history, medical history, and drug history were obtained through a self-administered questionnaire. The data from Huntingdon came from a nested case-control study, whereas in Chichester data were entered for all subjects who participated in the first screening round. Data about all prescribed drugs were available for the Huntingdon patients, whereas for the Chichester patients data for only cardiovascular drugs were recorded in detail. We determined for every patient the exposure to each of the major types of antihypertensive drugs: beta blockers, calcium-channel blockers, and ACE inhibitors. Smoking status was classified into three categories: current smokers, ex-smokers, and nonsmokers. Subjects were classified as nonsmokers if they had never smoked and as current-smokers if they were still smoking. A positive history of ischemic heart disease was recorded if the patient had sustained a myocardial infarction, had been admitted to a hospital for treatment of angina, or had undergone a coronary bypass operation. In both centers, blood pressure was measured automatically with a Dinamap 1846 SXP (Critikon, Kettering, UK).

The growth data analyzed from both studies consisted of age at first screen, and date and aortic diameter for all follow-up scans. A summary of the follow-up data from both centers has been published previously.[27] The average length of follow-up was 4 years (range, 6 months to 8 years). Each case was followed up with 6 monthly ultrasound scans. Growth was calculated by determining the difference between first and last diameter and dividing this difference by the length of follow-up in years.

Aortic elasticity was measured by M-mode ultrasound scanning in the majority of subjects in Huntingdon by a single ultrasonographer. We used a Toshiba Capasee with a curvilinear 3.5 MHZ probe (Toshiba Medical Systems Ltd, Crawley, UK).[28] The elasticity was measured in the infrarenal aorta at the same site that the diameter measurement was obtained. The aortic diameter in systole and in diastole was determined by freezing the M-mode picture if a clear trace was obtained. In each patient, three measurements were taken within 5 minutes of one other. The average of three measurements was used for the stiffness calculations. The elasticity of the aorta can be described as pressure strain elastic modulus (Ep) or stiffness (β).[29] The stiffness index is used here because it is less dependent on pulse pressure.[30]

For the Huntingdon patients, a blood sample was taken for measurement of serum collagen turnover. Blood samples were taken at the time of the measurement of aortic diameter and stiffness. The samples were centrifuged and the serum frozen at −20° C on the same day for analysis at a later date. Batches of 80 serum samples were analyzed by a single biochemist of the department of chemical pathology at Hinchingbrooke hospital. The concentration of the amino-terminal propeptide of type III procollagen (PIIINP) was used as a proxy measurement of type III collagen turnover, given that the aminoterminal propeptide is split from the procollagen molecule during type III collagen synthesis.[31] The concentration of PIIINP was measured by using an equilibrium type serum radioimmunoassay of the amino-terminal propeptide of type III procollagen on the basis of a highly purified specific human antigen (Pharmacia & Upjohn Ltd, Diagnostics Division, Milton Keynes, UK). We used duplicate 200-μL aliquots of serum according to the instructions of the manufacturer.[32,33] The intraassay and interassay coefficients of variation of this assay are less than 5% and the sensitivity is 0.2 μg/L. The reference range for adults, based on data of Finnish blood donors was 1.7 to 4.2 μg/L, with no differences between men and women.[32]

Statistical analysis. Statistical analysis was performed by using unconditional logistic regression methods to adjust for differences in age, gender, height, weight, place of measurement, smoking status, blood pressure, history of claudication, history of ischemic heart disease, and treatment for hypertension.[34] Hypotheses were tested by referring the log likelihood ratio to the χ^2 distribution, or using the *t* test to compare mean values. We used STATA 5.0 for Macintosh for all statistical analyses (Stata Corporation, College Station, Texas).

RESULTS

Data for 5811 subjects were available for analysis: 2775 men and 3036 women. There were 438 cases with aortic diameters larger than 29 mm and 5373 controls; 210 cases came from Huntingdon and 228 from Chichester; 237 controls were from Huntingdon and 5136 controls came from Chichester. In Huntingdon, only men were screened, whereas men and women were screened in Chichester. Ninety-one percent of cases were men and 9% women, whereas 45% of the controls were men and 55% were women. Data for cases and controls are shown in Table I. The differences between cases and controls in height and weight can be explained in part by differences in proportion of men and women between cases and controls. The differences in diastolic blood pressure, however, were mainly determined by place of measurement. Men in Huntingdon had a significantly higher diastolic blood pressure than men in Chichester: mean 84.8 mm Hg (95% confidence interval [CI], 84.8-86.1 mm Hg) in Huntingdon compared to 79.4 mm Hg (95% CI, 78.9-79.9 mm Hg) in Chichester. Systolic blood pressure did not differ markedly between the

Table I. Main characteristics of cases and controls

Variable	*Men*			*Women*		
	Cases	*Controls*	P	*Cases*	*Controls*	P
Number	397	2414		41	2995	
Age (y)	72	72	.78	74	72	.03
Current smoker	37%	9%	< .001	0%	1%	.051
Ex-smoker	53%	71%	< .001	63%	45%	.051
Nonsmoker	10%	21%	< .001	37%	54%	.051
On antihypertensive drugs	32%	21%	.002	34%	25%	.36
Mean systolic blood pressure (mm Hg)	158	155	.03	168	163	.26
Mean diastolic blood pressure(mm Hg)	85	80	< .001	83	79	.05
History of ischemic heart disease	21%	10%	< .001	15%	5%	.009
History of claudication	19%	12%	< .001	32%	12%	<.001
Mean height (cm)	173	172	.001	161	158	.01
Mean weight (kg)	80	75	< .001	64	63	.65

Data are percentages unless otherwise indicated. Cases were defined as subjects with an aortic diameter >29 mm; 210 cases came from Huntingdon and 228 from Chichester; 237 controls were from Huntingdon and 5136 controls came from Chichester. In Huntingdon only men were screened, whereas in Chichester men and women were screened.

Table II. Relative risk of having an AAA

Drug	*n*	*Exposed controls*	*Exposed cases*	*Crude OR*	*95% CI*	*Adjusted OR*	*95% CI*
Ca channel blocker	5811	260 (5)	62 (14)	3.2	2.4-4.4	2.6	1.5-4.3
ACE inhibitors	5811	179 (3)	28 (6)	2	1.3-3.0	0.7	0.3-1.5
Beta blockers	5811	664 (12)	86 (20)	1.7	1.4-2.2	0.6	0.4-1.1
Diuretics	5811	474 (9)	66 (15)	1.8	1.4-2.4	0.9	0.6-1.6

Data are n (%). Adjusted odds ratios were calculated using a logistic regression model adjusting for age, sex, screening program, height, weight, diastolic blood pressure, smoking status, history of ischemic heart disease, history of claudication, and drug treatment for hypertension.

Table III. Growth rates

Drug	*Exposed*		*Not exposed*		P
	n	*growth/year*	*n*	*growth/year*	
Calcium channel	48	0.5 (0-1.1)	284	0.8 (0.5-1.1)	.52
ACE Inhibitors	24	0.02 (−0.6-0.7)	308	0.8 (0.5-1.1)	.18
Diuretics	54	0.8 (0.1-1.5)	278	0.7 (0.4-1.1)	.88
Beta blocker	77	0.8 (0.3-1.4)	255	0.7 (0.4-1.1)	.82

Growth rates in mm per year with 95% CI. *P* values calculated using the *t* test.

two places: 156.2 mm Hg (95% CI, 154.0-158.4 mm Hg) in men from Huntingdon compared to 155.7 mm Hg (95% CI, 154.6-156.8 mm Hg) in men from Chichester.

Crude and adjusted odds ratios, used to estimate the association between antihypertensive drugs and AAA, are shown in Table II. The association for all antihypertensive drugs, except calcium-channel blockers, disappeared when adjusted for age, gender, height, weight, place of measurement, smoking status, blood pressure, history of ischemic heart disease, history of claudication, and treatment for hypertension.

Longitudinal data of 216 cases from Huntingdon and 129 cases from Chichester were analyzed to investigate whether antihypertensive medication influences the expansion of AAA. Growth data were used for analysis if the measurements were at least 6 months apart. Table III shows the mean growth rates per year for cases exposed to certain antihypertensive drugs and nonexposed cases. No significant differences were found in growth rate between cases exposed to any of the main antihypertensive medications and those not exposed.

In 246 controls and 201 cases, a serum PIIINP measurement was available to assess type III collagen turnover. The mean collagen turnover in cases was 3.73 μg/L (95% CI, 3.53-3.93) compared to 3.65 g/L (95% CI, 3.49-3.81). This difference is not statistically significant ($P = .52$) and both mean values are in the normal range. There were no statistically significant differences in type III collagen turnover between subjects receiving calcium-channel blockers, diuretics, or betablockers and subjects not exposed to these drugs. However there was a marked increase in mean collagen turnover between subjects receiving ACE inhibitors compared to those not receiving ACE inhibitors (Table IV).

Table IV. Collagen turnover as measured by serum PIIINP concentration

Drug	*No. exposed*	*Mean PIIINP (g/L)*	*No. not exposed*	*Mean PIIINP (g/L)*	P
Calcium channel	45	3.53 (3.25-3.82)	368	3.70 (3.56-3.84)	.65
ACE Inhibitors	35	4.26 (3.73-4.79)	378	3.62 (3.49-3.76)	.007
Diuretics	64	3.95 (3.61-4.30)	349	3.63 (3.49-3.77)	.08
Beta blockers	77	3.80 (3.52-4.08)	336	3.65 (3.51-3.80)	.25

95% Confidence intervals of the mean between subjects exposed to classes of antihypertensive drugs and those not exposed. *P* values were calculated by applying the *t* test to the log transformation of the mean PIIINP.

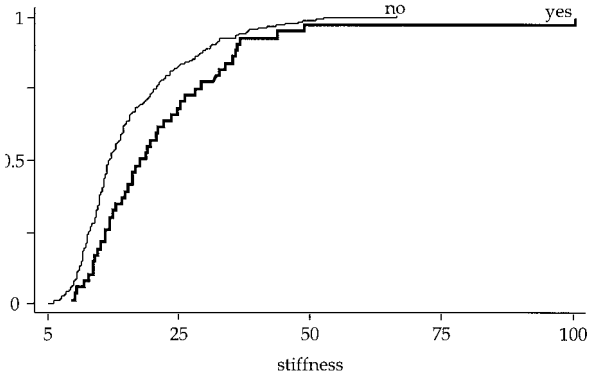

Fig 1. Cumulative frequency distribution graph of stiffness in cases exposed and not exposed to calcium-channel blockers. The cumulative probability (or percentiles) is depicted on the Y axis, and stiffness in arbitrary units on the X axis.

Measurements of the stiffness (β) of the aortic wall were made for 197 cases with an AAA and 253 controls. The mean stiffness for cases was 24.3 arbitrary units (95% CI, 22.3-26.3) compared to 16.3 (95% CI, 15.2-17.4) for controls ($P < .001$). The mean stiffness for all subjects exposed to calcium-channel antagonists was 25.1 (95% CI, 20.0-30.2) compared to 19.3 (95% CI, 18.1-20.4) for subjects not exposed to calcium-channel antagonists ($P < .01$). The mean stiffness for cases receiving calcium-channel antagonists was increased: 28.4 (95% CI, 21.1-35.5) compared to 23.9 (95% CI, 21.8-25.9) to cases not exposed to calcium-channel antagonists. However, the difference in mean stiffness between exposed and nonexposed cases did not reach statistical significance because of smaller numbers ($P = .11$). The entire frequency distribution curve for cases receiving calcium-channel antagonists is shifted to the right, indicating increased stiffness (Fig 1) in all cases exposed to calcium-channel blockers. We found decreased stiffness in cases receiving ACE inhibitors: the mean stiffness in cases receiving ACE inhibitors was 19.0 arbitrary units (95% CI, 13.9-24.0) compared to 25.2 (95% CI, 23.0-27.4) for cases not receiving ACE inhibitors ($P = .06$). The cumulative frequency distribution curve is shifted to the left for cases receiving ACE inhibitors. (Fig 2). The difference between all subjects exposed to ACE inhibitors and those not exposed was not statistically significant ($P = .28$) (Table V).

DISCUSSION

This study has shown that calcium-channel blockers are an independent risk factor for AAA. Unlike the association with other antihypertensive drugs, this association remained highly significant after adjusting for age, gender, height, weight, place of measurement, smoking status, blood pressure, history of claudication, history of ischemic heart disease, and treatment for hypertension. We found an increased stiffness in subjects exposed to calcium-channel blockers, a decreased stiffness in cases exposed to ACE inhibitors, and an increased collagen turnover in subjects exposed to ACE inhibitors.

It seems unlikely that these results are chance findings because all were highly significant. Selection bias was minimized because cases and controls were selected from the same population. A possible source of bias lies in the fact that data were derived from two separate populations. However, both screening programs were community-based and both districts are predominantly rural and have an elderly, fairly affluent, and almost exclusively white population. A confounding factor is that in Huntingdon only men were screened, whereas in Chichester men and women were screened, and aneurysms are more prevalent in men than in women. Confounders on the basis of gender or differences in measurement methods between the two centers were all taken into account when interpreting the results. For instance, a large part of the differences in height and weight between cases and controls can be explained by gender differences. The differences in diastolic blood pressure may have been caused by different measurement methods in both places. We adjusted for gender, place of measurement, height, weight, and blood pressure in a logistic regression model to correct for spurious differences caused by these confounders.

Subjects with an aneurysm are more likely to have a history of ischemic heart disease, peripheral vascular disease, or hypertension than are subjects without an aneurysm.[23] Cases are, therefore, more likely to be taking antihypertensive medication than controls. We adjusted for treatment of hypertension, history of ischemic heart disease, and history of claudication. The association between calcium-channel blockers and AAA was independent of those confounders. Research in a porcine aneurysm model has shown that the calcium-channel antagonist amlodipine enhances elastase.[19] This could explain the strong indepen-

Table V. Stiffness measurements of the arterial wall made by M-mode ultrasound according to exposure to antihypertensive drugs.

Drug	*No. exposed*	*Mean stiffness*	*No. not exposed*	*Mean stiffness*	P
Calcium channel	45	25.1 (20.0-30.2)	364	19.3 (18.1-20.4)	.01
ACE inhibitors	31	18.1 (14.0-22.3)	378	20.0 (18.8-21.3)	.28
Beta blockers	77	21.6 (18.6-24.6)	332	19.5 (18.2-20.8)	.24
Diuretics	42	20.1 (16.6-23.6)	366	19.9 (18.6-21.1)	.69

P values were calculated by applying the *t* test to the log transformation of the mean stiffness.

dent association between the calcium-channel blockers and risk of developing an AAA.

Elastolysis is considered to be the primary event in aneurysm formation.[35-41] It seems plausible that risk factors associated with the initial development of aneurysms may be different from those associated with further expansion. The association of calcium-channel blockers with risk of small aneurysms and the increased stiffness seen in subjects receiving calcium-channel blockers support the theory that calcium-channel blockers are an initiating risk factor, affecting the function of elastin. This would also explain the similar levels of collagen turnover between subjects exposed to calcium-channel blockers and nonexposed subjects. Calcium-channel blockers may be an important risk factor for the initial development of aneurysms. No differences in growth were observed. However, data about duration of exposure to antihypertensive medication were not available. Furthermore, the observation period may be too short to see differences in growth in these small aneurysms. This study lacks sufficient power to make firm statements about the effect of antihypertensive medication on growth of small aneurysms.

ACE inhibitors showed the opposite risk factor profile. A marked increased collagen turnover was seen in subjects receiving ACE inhibitors and a significantly decreased stiffness in cases exposed to ACE inhibitors, but not for controls. The increased stiffness just failed to reach significance at the 5% level, so this could be a chance finding. However, the numbers were very small and the increased collagen turnover was highly significant. Furthermore, both findings are in keeping with each other. There is a biological explanation for the effect of ACE inhibitors on aneurysms because ACE inhibitors were specifically designed to bind zinc, which is an essential cofactor for some of the MMPs implicated in the metabolism of elastin or collagen.[22] Zinc is a known inhibitor of elastase, whether it also inhibits some of the tissue inhibitors of MMPs is unknown.[42] This may explain our finding that ACE inhibitors increase collagen turnover and decrease stiffness in small aneurysms. We could not confirm an effect on growth rate of small aneurysms because the majority of our aneurysms are small and have no or very limited expansion rates. The observation period is too short to see differences in growth in small aneurysms. The numbers of patients on ACE inhibitors were very small, so this study lacks power to detect a significant difference in growth between cases exposed to ACE inhibitors and those who are not.

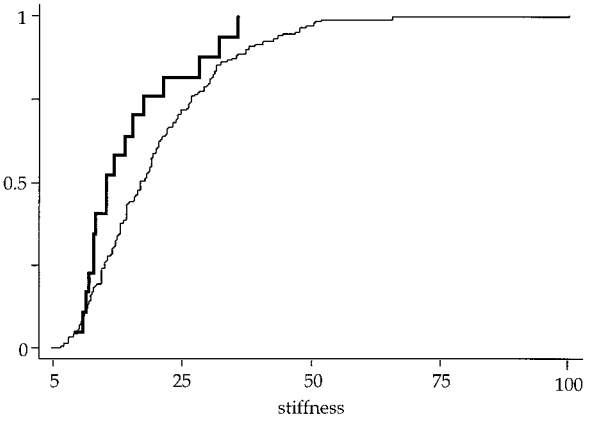

Fig 2. Cumulative frequency distribution graph of stiffness in cases exposed and not exposed to ACE inhibitors. The cumulative probability (or percentiles) is depicted on the Y axis and stiffness in arbitrary units on the X axis.

The clinical implications of this study for the management of patients with aneurysms who have hypertension or cardiac failure are uncertain. This study shows that calcium-channel blockers are an independent risk factor for the development of AAA. Effects on growth were not seen, but larger studies may be required to show such effects. It seems likely that the effect of calcium-channel blockers on aneurysms is an initiating effect, since they mainly affect elastin metabolism. Therefore, we would suggest selection of a beta blocker or a diuretic, and not a calcium-channel blocker, as the first choice in treatment for patients with hypertension and a strong family history of AAA. The effect of calcium-channel blockers on aneurysms, that require an operation, is likely to be less pronounced, as collagen degradation becomes more important in larger aneurysms.[43] Betablockers significantly reduce cardiac mortality after major vascular surgery.[44,45] It may, therefore, be prudent to switch a patient, who needs an AAA repair, from a calcium-channel blocker to a beta blocker if the calcium-channel antagonist was prescribed for hypertension only and not for angina. Further studies are needed to investigate the effect of ACE inhibitors on aneurysms before any recommendations can be made.

CONCLUSION

This study has shown that calcium-channel blockers are an independent risk factor for abdominal aortic aneurysms. Calcium channel blockers were associated with an increase in the arterial wall stiffness. ACE inhibitors were associated with an increase in type III collagen turnover. No significant effect of antihypertensive drugs on growth of small aneurysms was detected.

A.B.M.Wilmink, MD, was supported by a Health Services Research grant from the Anglia and Oxford Regional Health Authority. The Huntingdon Aneurysm Screening project is supported by the Anglia and Oxford Regional Health Authority and the British Heart Foundation. The authors are grateful to Nichola Lovell for the immaculate administration of the screening program, to Sharon Plaza for the stiffness measurements, and to Chris Marshall (Department of Chemical Pathology, Hinchingbrooke Hospital) for the accurate analysis of the PIINP assays.

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Submitted Feb 25, 2002; accepted Apr 29, 2002.